

## Trypsin Treatment Unlocks Bat Coronavirus Infection

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Vineet D. Menachery and Kenneth H. Dinnon are co-first authors. Order was determined by project originator.

**ABSTRACT** Traditionally, the emergence of coronaviruses is limited to a gain in receptor binding in a new host. Our previous work with acute respiratory syndrome (SARS)-like viruses argued that the ability to infect humans without adaptation. These findings suggest that additional barriers limit the emergence of zoonotic CoV. Here, we show that overcoming host restriction of two Middle East respiratory syndrome (MERS)-like CoVs using exogenous protease treatment. We found that the PDF2180-CoV, a MERS-like virus found in a Ugandan bat, could infect Vero and human cells in the presence of exogenous trypsin. These results suggest that the bat virus spike can mediate the infection of human cells to infect human lung cells. Using receptor-blocking antibodies, we show that infection with the PDF2180 spike does not require MERS-CoV receptor DPP4 and antibodies.

**Citation** Menachery VD, Dinnon KH, III, Yount BL, Jr, McAnarney ET, Gralinski LE, Hale A, Graham RL, Scobey T, Anthony SJ, Wang L, Graham B, Randell SH, Lipkin WI, Baric RS. 2020. Trypsin treatment unlocks barrier for zoonotic bat coronavirus infection. *J Virol* 94:e01774-19. <https://doi.org/10.1128/JVI.01774-19>.

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## Trypsin Treatment Unlocks Barrier for Zoonotic Bat Coronavirus Infection

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Vineet D. Menachery and Kenneth H. Dinnon are co-first authors. Order was determined by project originator.

binding domain and S2 portion are ineffective. Instead, we found that the addition of exogenous trypsin, not receptor binding, is the primary infection step. These results suggest that proteolytic cleavage is the primary infection step for zoonotic CoV strains.

These results suggest that proteolytic cleavage is the primary infection step for zoonotic coronaviruses. Moving forward, the ability to overcome host restriction and proteolytic cleavage of the spike are critical for evaluating the emergence potential and host range of zoonotic coronavirus strains and argue that the bat virus spike could be a site for future coronavirus research.

**Keywords:** emergence, spike, zoonotic

As public health infrastructures have been challenged by emerging and reemerging zoonotic viral diseases, understanding the mechanisms of zoonotic outbreaks (1). Severe acute respiratory

**Citation** Menachery VD, Dinnon KH, III, Yount BL, Jr, McAnarney ET, Gralinski LE, Hale A, Graham RL, Scobey T, Anthony SJ, Wang L, Graham B, Randell SH, Lipkin WI, Baric RS. 2020. Trypsin treatment unlocks barrier for zoonotic bat coronavirus infection. *J Virol* 94:e01774-19. <https://doi.org/10.1128/JVI.01774-19>.  
**Editor** Tom Gallagher, Loyola University Chicago

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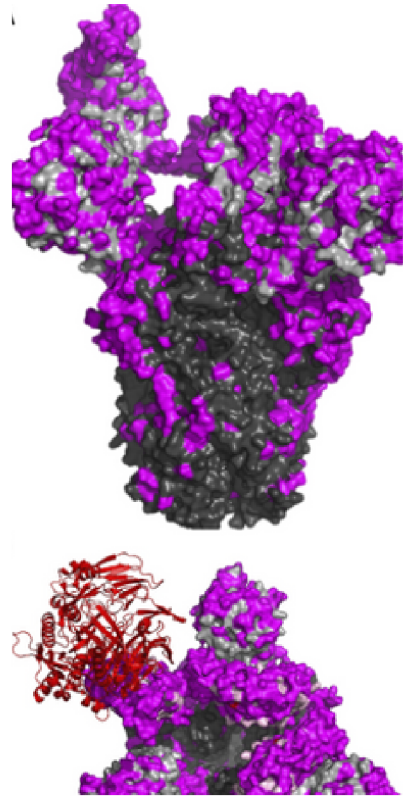
**Ian Lipkin,  
Ralph Baric,  
Lingshu Wang,  
Barney Graham**

**ABSTRACT** Traditionally, the emergence of zoonotic coronaviruses is attributed to a gain in receptor binding ability and the ability to infect humans.

serologic responses during the early stages of the MERS-CoV outbreak. Similarly, reverse genetics systems permitted the exploration of zoonotic coronaviruses (8); using the known SARS spike/ACE2 receptor interaction, chimeric viruses containing the backbones of bat CoVs were generated to evaluate the efficacy of both vaccines and therapeutics (9–12). The inverse approach placed the zoonotic spike proteins in the

addition of additional barriers limit the emergence of zoonotic CoV. In this work, we describe overcoming host restriction of two Middle East respiratory syndrome (MERS)-like bat CoVs using exogenous protease treatment. We found that the spike protein of PDF2180-CoV, a MERS-like virus found in a Ugandan bat, could mediate infection of Vero and human cells in the presence of exogenous trypsin. We subsequently show that the bat virus spike can mediate the infection of human gut cells but is unable to infect human lung cells. Using receptor-blocking antibodies, we show that infection with the PDF2180 spike does not require MERS-CoV receptor DPP4 and antibodies developed against the MERS spike receptor-binding domain and S2 portion are ineffective in neutralizing the PDF2180 chimera. Finally, we found that the addition of exogenous trypsin also rescues HKU5-CoV, a second bat group 2c CoV. Together, these results indicate that proteolytic cleavage of the spike, not receptor binding, is the primary infection barrier for these two group 2c CoVs. Coupled with receptor binding, proteolytic activation offers a new parameter to evaluate the emergence potential of bat CoVs and offers a means to recover previously unrecoverable zoonotic CoV strains.

We next examined the capacity of the MERS-Uganda spike to infect human respiratory cells, the primary targets of SARS-CoV, MERS-CoV, and other common cold-causing human CoVs. Using Calu3 cells, a human lung epithelial cell line, we observed robust replication of wild-type MERS-CoV based on RFP expression, consistent with previous studies (19). However, no evidence of infection was noted in MERS-Uganda-infected Calu3 cells in the presence or absence of trypsin. We subsequently explored infection of primary human airway epithelial (HAE) cultures. Grown on an air-liquid interface, HAE cultures have a propensity to facilitate improved infections of several human CoVs and may be more permissive for infection with the PDF-2180 spike chimera (22). To infect, PDF-2180 chimeric virus grown in the presence of trypsin was inoculated onto the apical surface of the HAE culture; cultures were subsequently



reverse genetics systems permitted the exploration of zoonotic coronaviruses (8); using the known SARS spike/ACE2 receptor interaction, chimeric viruses containing the backbones of bat CoVs were generated to evaluate the efficacy of both vaccines and therapeutics (9–12). The inverse approach placed the zoonotic spike proteins in the context of the epidemic SARS-CoV backbone (13, 14). These studies provided insight into potential threats circulating in bats as well as the efficacy of current therapeutic treatments (15). While far from comprehensive, the results indicated that these approaches, reagents, and predictions may prove useful in preparations for future CoV outbreaks.

## MATERIALS AND METHODS

**Cells, viruses, *in vitro* infection, and plaque assays.** Vero cells were grown in Dulbecco's modified Eagle medium (DMEM; Gibco, CA) supplemented with 5% FetalClone II (HyClone, UT) and antibiotic/antimycotic (anti/anti) (Gibco). Huh7 cells were grown in DMEM supplemented with 10% FetalClone II and anti/anti. Caco-2 cells were grown in MEM (Gibco) supplemented with 20% fetal bovine serum (HyClone) and anti/anti. Human airway epithelial cell (HAE) cultures were obtained from the University of North Carolina (UNC) Cystic Fibrosis (CF) Center Tissue Procurement and Cell Culture Core from human

**Biosafety and biosecurity.** Reported studies were initiated after the University of North Carolina Institutional Biosafety Committee approved the experimental protocols. All work for these studies was performed with approved standard operating procedures (SOPs) and safety conditions for MERS-CoV and other related CoVs. Our institutional CoV BSL3 facilities have been designed to conform to the safety requirements recommended by Biosafety in Microbiological and Biomedical Laboratories (BMBL), the U.S. Department of Health and Human Services, the Public Health Service, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH). Laboratory safety plans have been submitted, and the facility has been approved for use by the UNC Department of Environmental Health and Safety (EHS) and the CDC.

**Accession number(s).** The nearly complete genome sequence for MERS-CoV EMC (GenBank accession number [JX869059](#)) and PREDICT/PDF-2180 (GenBank accession number [KX574227](#)) were previously deposited in GenBank (16, 59).

# February 12, 2020

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**From:** Su, Lishan <[lishan\\_su@med.unc.edu](mailto:lishan_su@med.unc.edu)>

**Sent:** Wednesday, February 12, 2020 1:12 AM

**To:** Baric, Ralph S <[rbaric@email.unc.edu](mailto:rbaric@email.unc.edu)>

**Subject:** A commentary on 2019 nCoV vs lab engineered viruses

Hi Ralph:

In response to the EMI journal editor's request, Drs. Shan-Lu Liu, Lin Saif and myself are writing a commentary (1-2 pages) to dispute the rumors of 2019 nCoV origin. Will you be interested, and have time, to have a quick read/comment? Please let me know if you have time.

Tentative Title: Is 2019-nCoV laboratory origin?

Thanks!

-Lishan

# February 12, 2020

**From:** [Saif, Linda](#)  
**To:** [Liu, Shan-Lu](#); [lishan\\_su@med.unc.edu](mailto:lishan_su@med.unc.edu)  
**Subject:** FW: A commentary on 2019 nCoV vs lab engineered viruses  
**Date:** Wednesday, February 12, 2020 1:28:39 PM  
**Attachments:** [EMI-2019-nCoV\\_Commentary\\_LJS\\_SLL\\_Refs-rsb.docx](#)

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Hi

Please note that Ralph made these changes on an earlier copy sent to him so hopefully the 2 of you can incorporate them into the updated draft I sent this AM!

Regards,

Linda

Linda J. Saif, PhD  
Distinguished University Professor  
Food Animal Health Research Program  
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# February 12, 2020

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**From:** Su, Lishan <[lishan\\_su@med.unc.edu](mailto:lishan_su@med.unc.edu)>

**Sent:** Wednesday, February 12, 2020 10:11 AM

**To:** Baric, Ralph S <[rbaric@email.unc.edu](mailto:rbaric@email.unc.edu)>

**Subject:** Re: A commentary on 2019 nCoV vs lab engineered viruses

Hi Ralph:

We are trying to finish it and had no plan to get you too involved, but I do value your input. It is almost final and we are also getting comments from Perlman and Weiss.  
Thanks,

-Lishan

---

**From:** "Baric, Ralph S" <[rbaric@email.unc.edu](mailto:rbaric@email.unc.edu)>

**Date:** Wednesday, February 12, 2020 at 10:02 AM

**To:** "Su, Lishan" <[lishan\\_su@med.unc.edu](mailto:lishan_su@med.unc.edu)>

**Subject:** RE: A commentary on 2019 nCoV vs lab engineered viruses

sure, but don't want to be cited in as having commented prior to submission.

To: Baric, Ralph S[rbaric@email.unc.edu]  
From: Peter Daszak[daszak@ecohealthalliance.org]  
Sent: Tue 3/17/2020 10:03:52 AM (UTC-04:00)  
Subject: Follow up to the National Academies meeting we did in February  
[SC on EID and 21st Century Threats - One Pager.pdf](#)  
[Standing Committee on EIDs and 21st C Health Threats. Details.pdf](#)

Hi Ralph,

Just wanted to let you know that the National Academies did set up a Standing Committee as requested by the OSTP Director, who's on the President's COVID taskforce. It's called the "Standing Committee on Emerging Infectious Diseases & 21<sup>st</sup> Century Health Threats". The charge to the committee is attached. NASEM put out a call and I was nominated. I got some questions from NAM about my relationship to the Wuhan lab, but I explained that it's purely academic (no funds from China to me), and I offered to recuse myself from any discussions about the conspiracy theories re. lab release or bioengineering. The NASEM staff were ok with that and I joined the Committee. There was a meeting to discuss research agenda for COVID-19 and a doc has been written up on this for the OSTP. The meeting had a public session. I've attached the agenda, and details of who's on the committee (provisional, but we are prob now all approved).

Just wanted to let you know what's happening. I don't think this committee will be getting into the lab release or bioengineering hypothesis again any time soon – White House seems to be satisfied with the earlier meeting, paper in Nature and general comments within scientific community. National Security staff were in the room with OSTP on the first call.

Cheers,

Peter

Peter Daszak  
President

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*EcoHealth Alliance develops science-based solutions to prevent pandemics and promote conservation*



## First Meeting of the Standing Committee on Emerging Infectious Diseases and 21<sup>st</sup> Century Health Threats

### Final Agenda

Wednesday, March 11, 2020, 12:00 p.m. – 5:30 p.m. ET  
Virtual Zoom Meeting/Keck 201 for Local Participants

#### Background:

In response to a request from the Office of Science and Technology Policy (OSTP) and the Office of the Assistant Secretary for Preparedness and Response (ASPR), the National Academies of Sciences, Engineering, and Medicine will convene a standing committee of experts to help inform the federal government on critical science and policy issues related to emerging infectious diseases and other 21<sup>st</sup> century health threats. The standing committee will include members with expertise in emerging infectious diseases, public health, public health preparedness and response, biological sciences, clinical care and crisis standards of care, risk communication, epidemiology, and regulatory issues, as well as veterinary science, One Health, ethics, and community engagement. The standing committee will provide a venue for the exchange of ideas among federal government agencies, the private sector, and the academic community, as well as other relevant stakeholders.

#### Meeting Objectives

- Discuss the statement of task (SOT) and role of the standing committee
- Conduct the bias and conflict of interest discussion
- Discuss relevant context and key issues
- Explore potential research priorities arising as a result of the emergence of COVID-19 in the U.S. and globally
- Discuss next steps to move forward on key issues; plan second meeting and identify speakers and topics

Wednesday, March 11, 2020

#### CLOSED SESSION (COMMITTEE MEMBERS ONLY)

12:00 p.m.

#### Welcome and Introductions

- Brief introductions
- Discussion of meeting objectives

*The National Academies of*  
SCIENCES • ENGINEERING • MEDICINE

**STANDING COMMITTEE ON  
EMERGING INFECTIOUS DISEASES  
AND 21<sup>ST</sup> CENTURY HEALTH  
THREATS**

**Health and Medicine Division**

**Board on Health Sciences Policy  
Board on Global Health**

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**Briefing Materials  
Meeting 1  
March 11, 2020**

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Virtual Meeting

For committee use only—Do not circulate

**David Relman, M.D.**  
Thomas C. and Joan M. Merigan Professor of  
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President  
National Academy of Sciences

**Victor Dzau**  
President  
National Academy of Medicine

**Gregory Symmes**  
Chief Program Officer  
The National Academies of Sciences, Engineering, and Medicine

**Sponsors' Charge to the Committee**

- Discuss the context/purpose for the standing committee
- Review the statement of task

**Kelvin Droegemeier**  
Director  
White House Office of Science and Technology Policy

**David (Chris) Hassell**  
Senior Science Advisor  
Assistant Secretary for Preparedness and Response  
U.S. Department of Health and Human Services

**Committee Discussion with the Sponsor**

**Harvey Fineberg, Committee Chair**  
President  
Gordon and Betty Moore Foundation

*The National Academies of*  
**SCIENCES • ENGINEERING • MEDICINE**

Health and Medicine Division

***Standing Committee on Emerging Infectious Diseases and 21<sup>st</sup> Century Health Threats***

**INTERNAL COMMITTEE ROSTER**

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**Peter Daszak, Ph.D.**  
President and CEO  
EcoHealth Alliance

Peter Daszak is President of EcoHealth Alliance, a US-based organization that conducts research and outreach programs on global health, conservation, and international development. Dr. Daszak's research has been instrumental in identifying and predicting the origins and impact of emerging diseases across the globe. He is one of the founders of the field of Conservation Medicine and has been instrumental in the growth of EcoHealth, One Health, and now Planetary Health. Dr. Daszak is a member of the National Academy of Medicine and Chair of the NASEM's Forum on Microbial Threats. He is a member of the NRC Advisory Committee to the US Global Change Research Program, the Supervisory Board of the One Health Platform, the One Health Commission Council of Advisors, the CEEZAD External Advisory Board, the Cosmos Club, and the Advisory Council of the Bridge Collaborative. He has served on the IOM Committee on global surveillance for emerging zoonoses, the NRC committee on the future of veterinary research, the International Standing Advisory Board of the Australian Biosecurity CRC; and has advised the Director for Medical Preparedness Policy on the White House National Security Staff on global health issues. Dr. Daszak is a regular advisor to WHO on pathogen prioritization for R&D. He received his Ph.D. in parasitic infectious disease from the University of East London.

**Jonna Mazet, D.V.M., M.P.V.M., Ph.D.**

Executive Director, One Health Institute  
UC Davis School of Veterinary Medicine

Jonna Mazet is a Professor of Epidemiology and Disease Ecology and Executive Director of the One Health Institute in the UC Davis School of Veterinary Medicine, where she focuses on global health problem solving, especially for emerging infectious disease and conservation challenges. Dr. Mazet is active in international One Health research programs, most notably in relation to disease transmission among wildlife, domestic animals, and people and the ecological drivers of disease emergence. Currently, she is the Global Director of a \$175 million viral emergence early warning project, named PREDICT, that has been developed with the US Agency for International Development's (USAID) Emerging Pandemic Threats Program. She was elected to the National Academy of Medicine in 2013 in recognition of her successful and innovative approach to emerging environmental and global health threats and serves on the National Academies' Forum on Microbial Threats, as well as chairs the Academies' One Health Work Group. Jonna joined the UC Global Health Institute Board of Directors as co-vice chair in April 2019. She holds a D.V.M., M.P.V.M., and Ph.D. from UC Davis.

**Tara O'Toole, M.D., M.P.H.**  
Executive Vice President  
In-Q-Tel


Tara O'Toole currently serves as Executive Vice President at In-Q-Tel. Dr. O'Toole was confirmed as the Under Secretary for Science and Technology (S&T) at the U.S. Department of Homeland Security (DHS) and served from November 4, 2009 to September 23, 2013. From 2003 to November 2009, Dr. O'Toole was the CEO and Director of the Center for Biosecurity at the University of Pittsburgh Medical Center (UPMC), and Professor of Medicine and of Public Health at the University of Pittsburgh. The Center for Biosecurity of UPMC is an independent organization dedicated to improving the country's resilience to major biological threats. Dr. O'Toole is internationally known for her work on biosecurity and on health and safety issues related to the U.S. nuclear weapons complex. Her publications in the biodefense field include articles on the response to anthrax, smallpox, and plague biological attacks; containment of contagious disease epidemics; biodefense research and development strategies; and hospital preparedness. She is the founding editor of the journal *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*. She was a principal author and producer of *Dark Winter*, an influential exercise conducted in June 2001 to alert national leaders to the dangers of bioterrorist attacks. She was also a principal writer and producer of *Atlantic Storm*, an international ministerial-level biosecurity exercise held in January 2005. Prior to founding the UPMC in 2003, Dr. O'Toole was one of the original members of the Johns Hopkins Center for Civilian Biodefense Strategies and served as its director from 2001 to 2003. She has served on numerous government and expert advisory committees dealing with biodefense, including panels of the Defense Science Board; the National Academy of Engineering Committee on Combating Terrorism; and the National Academy of Sciences Working Group on Biological Weapons. She served as chair of the Board of the Federation of American Scientists from 2006 to 2007, and in 2006 she was appointed to the board of Google Foundation's International Networked System for Total Early Disease

**Tara O'Toole, M.D., M.P.H.**  
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Detection. From 1993 to 1997, Dr. O'Toole served as Assistant Secretary of Energy for Environment Safety and Health. In this position, she was the principal advisor to the Secretary of Energy on environmental protection and on the health and safety of the approximately 100,000 workers in the U.S. nuclear weapons complex and Department of Energy (DOE) laboratories. She developed the first overall management and safety plan for dealing with the highly enriched uranium, plutonium, spent fuel, and radioactive waste left in place when nuclear weapons production was stopped in the early 1990s. She ran the multi-agency, multimillion-dollar task force that oversaw the government's investigations into human radiation experiments conducted during the Cold War and led the U.S. delegation to Russia to establish the U.S./Russia cooperative effort to study radiation exposure and environmental hazards of the Russian nuclear weapons complex. Prior to her work at DOE, Dr. O'Toole was a senior analyst at the Congressional Office of Technology Assessment, where she directed several projects and studies, including the health impact of pollution resulting from nuclear weapons production. She also served as a consultant to industry and government in matters related to occupational and environmental health; worker participation in workplace safety protection; and organizational change. Dr. O'Toole practiced general internal medicine in community health centers in Baltimore from 1984 to 1988. She is board certified in internal medicine and occupational and environmental health. She has a bachelor's degree from Vassar College, an M.D. from the George Washington University, and a Master of Public Health degree from Johns Hopkins University. She completed internal medicine residency training at Yale University and a fellowship in Occupational and Environmental Medicine at Johns Hopkins University.

# Standing Committee on EIDs & the 21st Century Health Threats

The key findings of the Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats were not explicitly provided in the search results. However, the committee was formed to respond to requests from the federal government to assess and consider the science and policy implications of emerging infectious diseases and 21st-century health threats, particularly in the context of the COVID-19 pandemic. The committee's work included rapid expert consultations on urgent questions such as crisis standards of care, diagnostic testing, and virus transmission, aiming to provide the best evidence available at the time to support the government's response to the pandemic <sup>1</sup> <sup>3</sup> <sup>4</sup> <sup>5</sup>. For specific key findings, referring to the committee's reports and publications would be necessary.



The purpose of the March 2020 National Academies of Sciences Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats was to provide a rapid response to the government on key coronavirus questions and crisis standards of care for the coronavirus pandemic. The committee was formed to respond quickly to requests from the federal government to assess and consider the science and policy implications of emerging infectious diseases and 21st-century health threats <sup>1</sup> <sup>3</sup> <sup>5</sup>. It aimed to provide the best evidence available at the time of each publication to support the government's response to the pandemic <sup>2</sup>.

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## **Standing Committee on EIDs & the 21st Century Health Threats**

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